

Theses of doctoral (Ph.D.) dissertation

NEW REACTIONS OF 2H-AZIRINES

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1. Introduction and Aims

Due to their exceptional reactivity arising from their strained ring system and their widespread applicability as precursors, *2H*-azirines are one of the most valuable building blocks in the synthetic chemist's toolbox. All three bonds can undergo selective cleavage on thermal or photochemical excitation to generate unstable vinyl nitrene, imino carbene or nitrile ylide species. Moreover, they can act as nucleophiles through the lone electron pair of the nitrogen, as electrophiles through the carbon atoms, and as dienophiles or dipolarophiles in cycloaddition reactions through the electron-rich π -bond, enabling the synthesis of various saturated and unsaturated heterocyclic as well as open-chain compounds.

Developing methods for the synthesis of large and diverse chemical libraries is one of the major aims of organic and medicinal chemistry research. Therefore, investigations on the novel applicability of such versatile precursors as *2H*-azirines towards the synthesis of either new aziridine derivatives or other biologically relevant heterocycles are still of interest.

The aim of this doctoral dissertation was the elaboration of unprecedented reactions of *2H*-azirines as electrophiles and dipolarophiles, namely,

- (i) the extension of the Ugi–Joullié three-component reaction to *2H*-azirines,
- (ii) a three-component reaction based on the 1,3-dipolar cycloaddition of *2H*-azirines and azomethine ylides generated from isatins,
- (iii) and the 1,3-dipolar cycloaddition of *2H*-azirines and nitrones.

We have focused on developing and optimizing such new synthetic methodologies, which enable the assembly of highly diverse heterocyclic compound libraries with arbitrary substitution patterns.

2. Materials and Methods

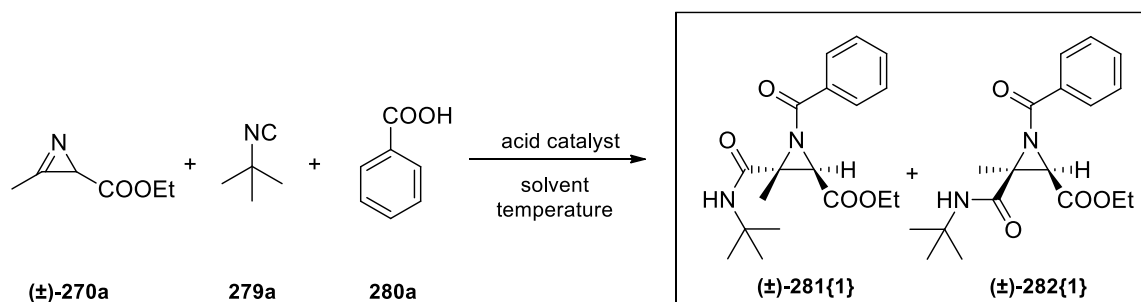
In the course of the synthetic work, the majority of the reactions were performed in a millimolar scale. Reactions were monitored either by thin-layer chromatography or HPLC analyses. Products were purified by column chromatography (silica), flash chromatography (silica), recrystallization or vacuum distillation. The molecular structures of products were determined by one- and two-dimensional NMR techniques combined with mass spectrometric measurements and occasionally by X-ray diffraction.

3. Results and Discussion*

3.1. A new method was developed for the synthesis of *N*-acylaziridine-2-carboxamides through the extension of the Ugi–Joullié three-component reaction to 2*H*-azirines.

A model reaction of (±)-ethyl 3-methyl-2*H*-azirine-2-carboxylate ((±)-**270a**), *tert*-butyl isocyanide (**279a**) and benzoic acid (**280a**) was investigated. The reaction required Lewis or Brønsted acid catalysis for the activation of the azirine and led to two *N*-acylaziridine-2-carboxamide diastereomers (products *trans*-(±)-**281**{1} and *cis*-(±)-**282**{1}) (Scheme 1). By testing different acid catalysts with varied catalyst loadings, solvent, temperature, and concentration, the optimal reaction conditions were set (25 mol% ZnCl₂, abs. THF, 0.125 M (±)-**270a**, argon, 55 °C, 4–6 h, 81% combined HPLC yield, 96:4 *trans*:*cis* dr). It was observed that the reaction conditions have no significant influence on the diastereomeric ratios.

The model reaction was also performed with optically active 2*H*-azirine (-)-(*R*)-**270a**. Epimerization or decrease in enantiomeric excess was not observed and the target compound (+)-(*2R,3R*)-**281**{1} was isolated with an optical purity (72% ee) identical to that of the precursor 2*H*-azirine, which was further increased (92% ee) by recrystallization.

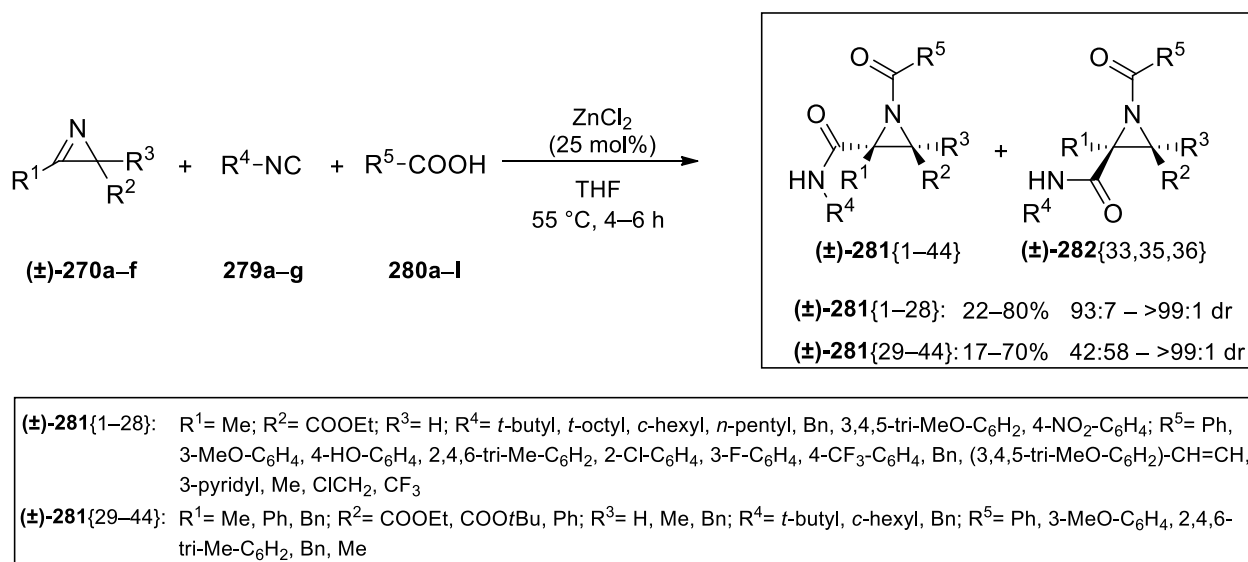


Scheme 1.

3.2. Systematically varying the carboxylic acid and isocyanide components of the model reaction, a 28-membered compound library was synthesized (Scheme 2). Benzoic acids bearing electron-donating and electron-withdrawing substituents as well as aralkyl, heteroaromatic, and aliphatic carboxylic acids were compatible with the reaction. Aliphatic, benzyl, and aromatic isocyanides could be also subjected to the reaction. Since the reactions proceeded with high diastereoselectivities (93:7 – >99:1 dr), the major *trans* products **281**{1–28} were isolated exclusively (22–80%). It was observed that the efficiency of the transformation is mainly affected by the electronic nature of the isocyanide. Benzyl and aliphatic isocyanides provided better isolated yields than aromatic derivatives.

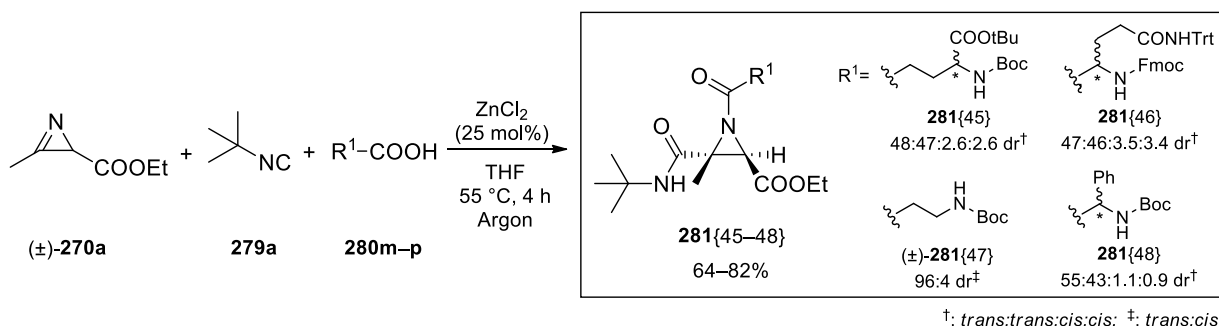
* Compound numbering is identical to that in the dissertation

By employing various *2H*-azirines, the *N*-acylaziridine-2-carboxamide library was further extended (**281**{29–44} and **282**{33,35,36}: 17–70%, 42:58 – >99:1 dr) (Scheme 2). Among others it was observed that the formation of the *trans* diastereomer is significantly decreased due to steric effects (42:58–63:37 *trans/cis* dr), if fully substituted azirines are applied. Besides, we found that the reaction could also be extended to aromatic *2H*-azirines with excellent diastereoselectivities (>99:1 dr).



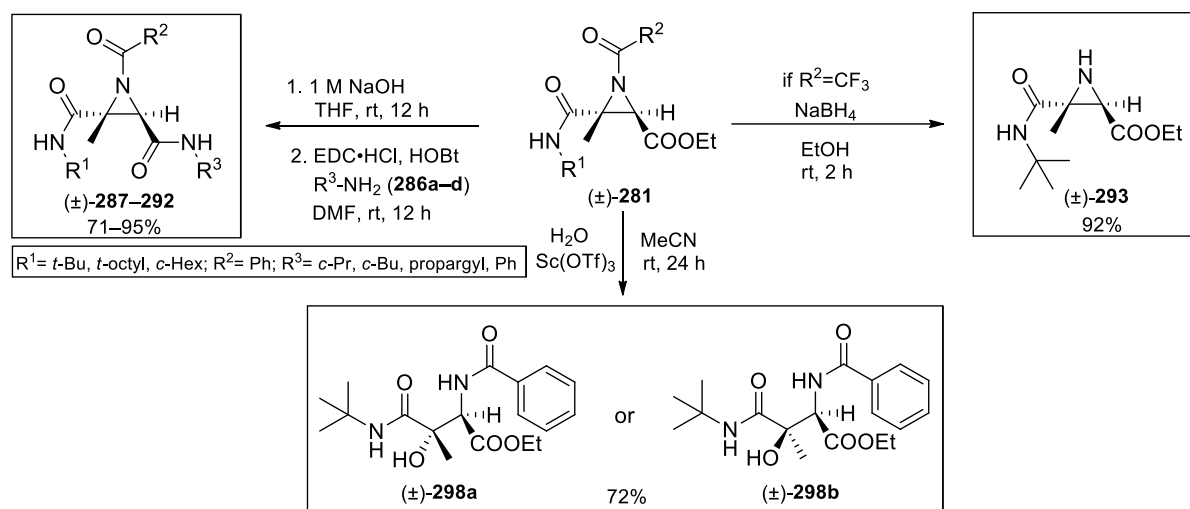
Scheme 2.

3.3. Reacting *N*-protected L-glutamic acid, L-glutamine, β-alanine, and D-phenylglycine as carboxylic acid components with azirine (**±**)-**270a** and *tert*-butyl isocyanide (**279a**), dipeptides **281**{45–48} were prepared (64–82%) (Scheme 3). The optically active amino acid components did not result in significant asymmetric induction; however, the major *trans* products were isolated as diastereomeric mixtures.



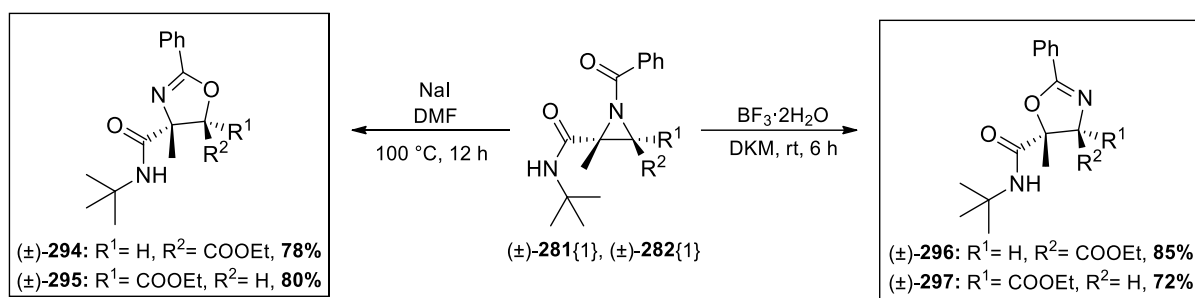
Scheme 3.

3.4. The utility of the synthesized *N*-acylaziridines was investigated through several derivatizations (Scheme 4 and Scheme 5). The ethoxycarbonyl group of *N*-benzoylaziridines (\pm)-**281**{1,11,12} was converted to carboxamide through alkaline ester hydrolysis followed by EDC/HOBt-mediated amide coupling with amines. The desired *N*-acylaziridine-2,3-dicarboxamide derivatives (\pm)-**287–292** were obtained in good yields (71–95%), proving that the electron-deficient aziridine ring withstands the conditions of the hydrolysis and coupling reaction. *N*-unsubstituted aziridine (\pm)-**293** was prepared through the removal of the *N*-trifluoroacetyl group from compound (\pm)-**281**{10}. Compound (\pm)-**281**{1} was transformed to β -hydroxy- α -amino acid derivative (\pm)-**298** with water in the presence of Sc(OTf)₃. Ring opening resulted in a single product with complete regioselectivity, although the diastereomeric outcome of the reaction could not be determined.



Scheme 4.

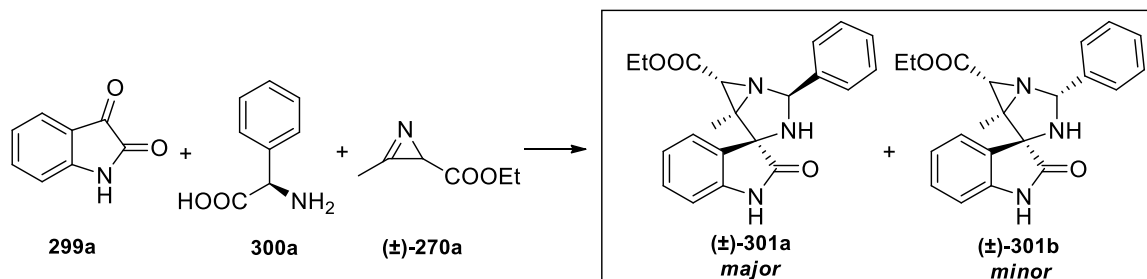
Starting from *trans*-(\pm)-**281**{1} and *cis*-(\pm)-**282**{1} *N*-benzoylaziridine diastereomers, oxazolines were synthesized *via* Heine reaction (Scheme 5, products *trans*-(\pm)-**294** and *cis*-(\pm)-**295**). Reactions performed with BF₃·2H₂O led to oxazolines as well, though with inversed regioselectivity (products *trans*-(\pm)-**296** and *cis*-(\pm)-**297**), instead of ring opening. The transformations were accomplished with complete regioselectivity and retention of configuration. None of the synthetic methods resulted in epimerization.



Scheme 5.

3.5. A novel three-component reaction was developed for the assembly of a new aziridine-fused spirooxindole-imidazolidine framework through the 1,3-dipolar cycloaddition of *2H*-azirines with azomethine ylides generated from isatins.

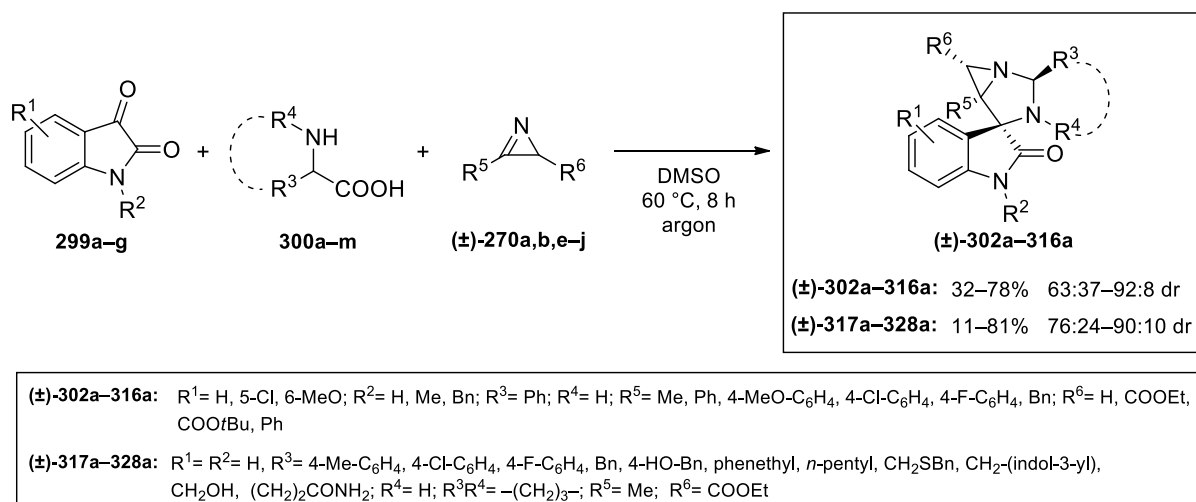
Investigation of the three-component reaction of isatin (**299a**), D-(-)-2-phenylglycine, and (±)-ethyl 3-methyl-*2H*-azirine-2-carboxylate ((±)-**270a**) led to the identification of two diastereomeric spirooxindole-imidazolidine *endo* cycloadducts (Scheme 6, compounds (±)-**301a** and (±)-**301b**). The reaction conditions were optimized by applying different solvents as well as varying the concentration and the temperature (DMSO, 0.25 M (±)-**270a**, 60 °C, 8 h; 72% combined HPLC yield, 92:8 dr). A plausible reaction mechanism was proposed.



Scheme 6.

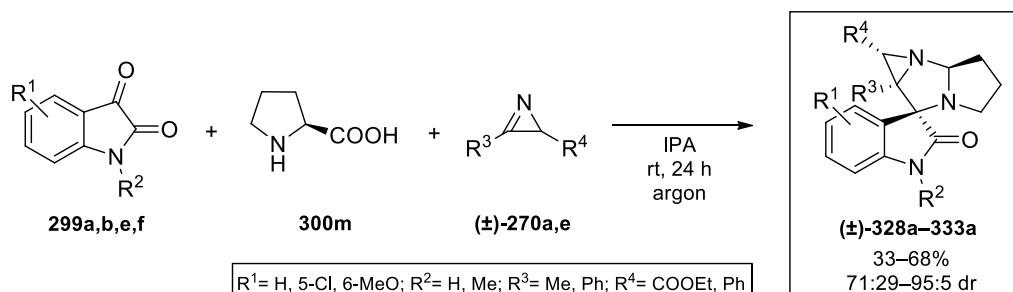
3.6. Systematically varying the isatin, then the *2H*-azirine components of the model reaction, a 15-membered compound library was synthesized (Scheme 7). The reactions proceeded with moderate to good diastereoselectivity (63:37–92:8 dr); therefore, the major isomer was isolated exclusively ((±)-**302a–316a**: 32–78%). Remarkable substituent effect was not observed, and both electron-rich and electron-deficient isatins and aromatic azirines were tolerated. Application of 3-benzyl-2-phenyl-*2H*-azirine resulted in the increased formation of the minor diastereomer (63:37 dr), which was accounted for by the π – π interaction between the benzyl moiety (R⁵) and the phenyl group of the azomethine ylide (R³ = Ph). The R⁶ substituent had negligible impact on the stereochemical outcome of the 1,3-dipolar cycloaddition.

Using a range of α -amino acids with isatin (**299a**) and azirine (\pm)-**270a** as inputs, the spirooxindole-imidazolidine library was extended by 12 derivatives (Scheme 7, compounds (\pm)-**317a–328a**). Amino acids bearing various aliphatic, aromatic, and aralkyl side chains as well as trifunctional amino acids were proved to be compatible with the reaction (37–81%); however, alicyclic L-proline resulted in remarkably low yield ((\pm)-**328a**: 11%). The nature of the amino acid component had no significant influence on the diastereoselectivity.



Scheme 7.

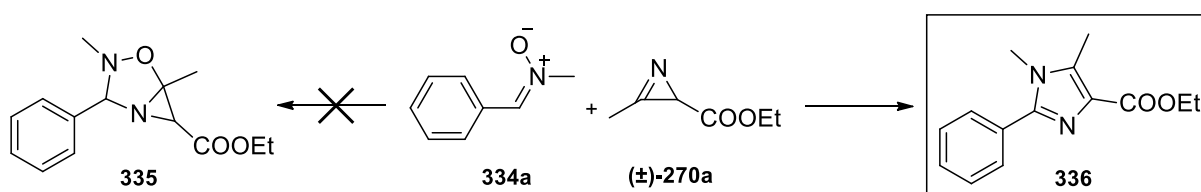
3.7. The reaction conditions for the synthesis of L-proline derivative (\pm)-**328a** was reinvestigated. By optimizing the solvent, concentration, temperature, and the equivalence of 2*H*-azirine, a significant increase in yield was achieved (IPA, 0.075 M **300m**, 3 equiv. of 2*H*-azirine, rt, 24 h, 68% HPLC yield). By applying the reoptimized protocol, five more spirooxindole-imidazolidine derivatives were synthesized (33–68%) mostly with high diastereoselectivities (71:29–95:5 dr) (Scheme 8).



Scheme 8.

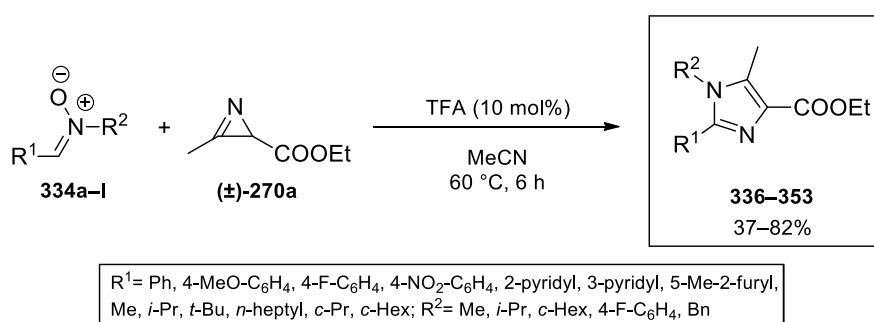
3.8. A new synthetic method was developed for the assembly of tetrasubstituted imidazoles by the elaboration of a 1,3-dipolar cycloaddition reaction between 2*H*-azirines and nitrones.

A model reaction of 2*H*-azirine (\pm)-**270a** and *N*-methylnitrone **334a** was investigated. We found that the reaction requires acid catalysis and leads to the formation of tetrasubstituted imidazole **336** instead of the expected cycloadduct **335** (Scheme 9). Among several Brønsted and Lewis acids tested, TFA proved to be the most efficient (**336**: 62% HPLC yield (rt)). By applying different solvents and varying the azirine and catalyst loading, the optimal reaction conditions were set (10 mol% TFA, abs. MeCN, 1.5 equiv. (\pm)-**270a**, 60 °C, 6 h, 78% HPLC yield). A plausible reaction mechanism was proposed.



Scheme 9.

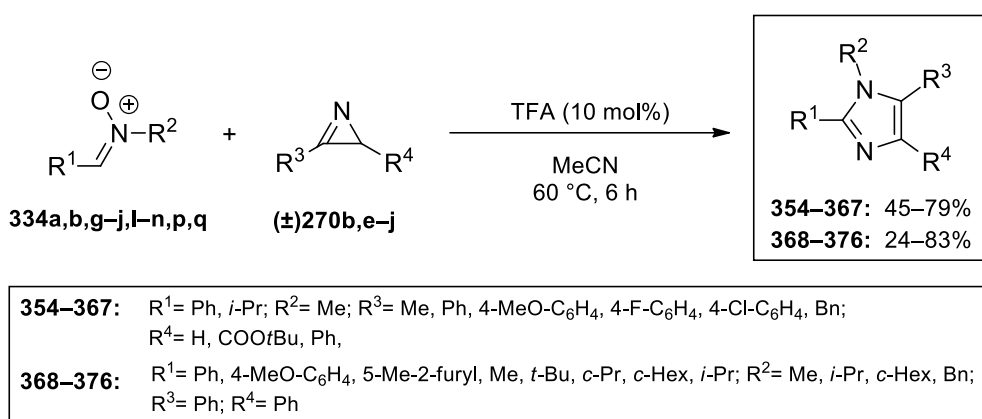
3.9. Reacting 2*H*-azirine (\pm)-**270a** with a range of nitrones, 18 tetrasubstituted imidazoles were synthesized (Scheme 10). Both electron-rich and electron-poor *C*-phenyl *N*-methylnitrones as well as *C*-heteroaromatic and *C*-aliphatic *N*-methylnitrones could be subjected to the reaction (41–82%). The reaction was also extended to *C*-phenyl and *C*-alkyl *N*-(aryl)alkyl and *N*-aliphatic nitrones (37–71%). It was found that the increase in the steric demand of the nitrone substituents generally resulted in lower isolated yields.



Scheme 10.

3.10. The applicability of different azirines was investigated, using both a *C*-aromatic (R^1 = phenyl) and a *C*-aliphatic (R^1 = *i*-Pr) *N*-methylnitrone as reaction partners (Scheme 11, compounds **354–367**). The method also enabled access to 4,5-diarylimidazoles affording good yields (67–79%) regardless of the electronic nature of the 2,3-diarylazirine. Lower isolated yields (45% and 57%) were achieved if 3-benzyl-2-phenyl-2*H*-azirine was employed, while the monosubstituted 3-phenyl-2*H*-azirine led to complex reaction mixtures and only trace amounts of imidazoles.

We investigated the reactivity of 2,3-diphenyl-2*H*-azirine toward some of the *C*-aryl and *C*-aliphatic as well as *N*-aliphatic and *N*-benzyl nitrones applied previously. As a result, nine more imidazole derivatives were synthesized (**368–376**: 24–83%) (Scheme 11). Nitrones bearing sterically more demanding substituents generally resulted in lower yields.



Scheme 11.

4. Scientific publications forming the basis of the doctoral dissertation

1. **A. Angyal**, A. Demjén, E. Wéber, A. K. Kovács, J. Wölfling, L. G. Puskás, I. Kanizsai
Lewis Acid-Catalyzed Diastereoselective Synthesis of Multisubstituted *N*-Acyl-aziridine-2-carboxamides from 2*H*-Azirines via Joullié–Ugi Three-Component Reaction
J. Org. Chem. **2018**, 83, 3570–3581.
IF: 4.745
2. **A. Angyal**, A. Demjén, V. Harmat, J. Wölfling, L. G. Puskás, I. Kanizsai
1,3-Dipolar Cycloaddition of Isatin-Derived Azomethine Ylides with 2*H*-Azirines: Stereoselective Synthesis of 1,3-Diazaspiro[bicyclo[3.1.0]hexane]oxindoles
J. Org. Chem. **2019**, 84, 4273–4281.
IF: 4.335
3. **A. Angyal**, A. Demjén, J. Wölfling, L. G. Puskás, I. Kanizsai
Acid-Catalyzed 1,3-Dipolar Cycloaddition of 2*H*-Azirines with Nitrones: An Unexpected Access to 1,2,4,5-Tetrasubstituted Imidazoles
J. Org. Chem. **2020**, 85, 3587–3595.
IF: 4.335
(2019)

Total IF: 13.415

5. Scientific publications not related to the doctoral dissertation

1. **A. Angyal**, A. Demjén, J. Wölfling, L. G. Puskás, I. Kanizsai
A green, isocyanide-based three-component reaction approach for the synthesis of multisubstituted ureas and thioureas
Tetrahedron Lett. **2018**, 59, 54–57.
IF: 2.328
2. A. Demjén, **A. Angyal**, J. Wölfling, L. G. Puskás, I. Kanizsai
One-pot synthesis of diverse *N,N'*-disubstituted guanidines from *N*-chlorophthalimide, isocyanides and amines via *N*-phthaloyl-guanidines
Org. Biomol. Chem. **2018**, 16, 2143–2149.
IF: 3.547
3. A. Demjén, R. Alföldi, **A. Angyal**, M. Gyuris, L. Hackler, G. Szebeni, J. Wölfling, L. Puskás, I. Kanizsai
Synthesis, Cytotoxic Characterization, and SAR Study of Imidazo[1,2-*b*]pyrazole-7-carboxamides
Arch. Pharm. Chem. Life Sci. **2018**, 351, e1800062.
IF: 2.108
4. A. Demjén, L. Puskás, I. Kanizsai, G. Szebeni, **A. Angyal**, M. Gyuris, L. Hackler
Imidazo-Pyrazole Carboxamide Derivatives as Anticancer Agents and the Synthesis Thereof
WO2019220155 (A1), **2019**.

Total IF: 7.983

6. Posters

1. **A. Angyal**, L. G. Puskás, J. Wölfling, I. Kanizsai
A Novel Isocyanide Coupling Reaction for the Synthesis of *N,N'*-Disubstituted Ureas
14th Belgian Organic Synthesis Symposium, Louvain-la-Neuve (Belgium), **2014**.
2. A. Demjén, **A. Angyal**, L. G. Puskás, J. Wölfling, I. Kanizsai
Novel Isocyanide-Based Approach for the Synthesis of *N,N'*-Disubstituted Guanidines through *N*-Phthaloylguanidines
27th European Colloquium on Heterocyclic Chemistry, Amsterdam (Netherlands), **2016**.
3. A. Demjén, R. Alföldi, **A. Angyal**, M. Gyuris, L. Hackler Jr., G. J. Szebeni, J. Wölfling, L. G. Puskás, I. Kanizsai
Synthesis and Cytotoxic Evaluation of Novel Imidazo[1,2-*b*]pyrazole-7-carboxamides
22th International Conference on Organic Synthesis, Florence (Italy), **2018**.
4. **A. Angyal**, A. Demjén, L. G. Puskás, J. Wölfling, I. Kanizsai
Lewis Acid-Catalyzed Diastereoselective Synthesis of Multisubstituted *N*-Acyl-aziridine-2-carboxamides from 2*H*-Azirines *via* Joullié–Ugi Three-Component Reaction
22th International Conference on Organic Synthesis, Florence (Italy), **2018**.